Effects of a Short Course of Eszopiclone on Continuous Positive Airway Pressure Adherence

A Randomized Trial

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Background: Adherence to short-term continuous positive airway pressure (CPAP) may predict long-term use. Unfortunately, initial CPAP intolerance may lead to poor adherence or abandonment of therapy.

Objective: To determine whether a short course of eszopiclone at the onset of therapy improves long-term CPAP adherence more than placebo in adults with obstructive sleep apnea.

Design: Parallel randomized, placebo-controlled trial from March 2007 to December 2008. Randomization, maintained and concealed centrally by pharmacy personnel, was computer-generated using fixed blocks of 10. Referring physicians, investigators, and patients were blinded to the treatment assignment until after the final data were collected. (ClinicalTrials.gov registration number: NCT00612157)

Setting: Academic sleep disorder center.

Patients: 160 adults (mean age, 45.7 years [SD, 7.3]; mean apnea–hypopnea index, 36.9 events/h [SD, 23]) with newly diagnosed obstructive sleep apnea initiating CPAP.

Intervention: Eszopiclone, 3 mg ($n = 76$), or matching placebo ($n = 78$) for the first 14 nights of CPAP.

Measurements: Use of CPAP was measured weekly for 24 weeks. Adherence to CPAP (primary outcome) and the rate of CPAP discontinuation and improvements in symptoms (secondary outcomes) were compared. Follow-up at 1, 3, and 6 months was completed by 150, 136, and 120 patients, respectively.

Results: Patients in the eszopiclone group used CPAP for 20.8% more nights (95% CI, 7.2% to 34.4%; $P = 0.003$), 1.3 more hours per night for all nights (CI, 0.4 to 2.2 hours; $P = 0.005$), and 1.1 more hours per night of CPAP use (CI, 0.2 to 2.1 hours; $P = 0.019$). The hazard ratio for discontinuation of CPAP was 1.90 (CI, 1.1 to 3.4; $P = 0.033$) times higher in the placebo group. Side effects were reported in 7.1% of patients and did not differ between groups.

Limitations: Patients had severe obstructive sleep apnea treated at a specialized sleep center with frequent follow-up; results may not be generalizable to different settings. Patients' tolerance to CPAP and their reasons for discontinuation were not assessed.

Conclusion: Compared with placebo, a short course of eszopiclone during the first 2 weeks of CPAP improved adherence and led to fewer patients discontinuing therapy.

Primary Funding Source: Sepracor.

Ann Intern Med. 2009;151:696-702. www.annals.org

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Untreated obstructive sleep apnea (OSA) is associated with adverse effects on both health and quality of life (1, 2). Continuous positive airway pressure (CPAP) is recommended as first-line therapy for most patients to improve sleep quality, reduce daytime sleepiness, and enhance quality of life. It may also mitigate the increased risk for cardiovascular events (3–6). However, adherence to CPAP is often poor, which limits its efficacy. Of patients who initiate CPAP, approximately 50% discontinue use within the first year, most within the first month. The initial experience with CPAP influences who accepts and continues treatment (7). Patients who experience initial discomfort, intolerance, or lack of perceived benefit are more likely to discontinue therapy (8). Some studies suggest that psychosocial factors may also affect short- and intermediate-term adherence (9, 10). The only consistently reliable predictor of long-term adherence has been the use of CPAP during the initial treatment period (11). The average nightly CPAP use during the first 3 months of therapy can predict use at 6 and 12 months (12). Furthermore, long-term adherence patterns may be determined within the first few days of therapy (13). Therefore, strategies aimed at improving adherence with therapy should focus on the initial experience with CPAP.

In theory, robust patient education, regular follow-up, and improvements in device comfort (for example, autoadjustable units with heated humidifiers and better-designed, better-fitted masks) should increase CPAP tolerance and use. However, intensive support and technological interventions have not consistently or reliably predicted which patients will successfully transition to CPAP (14–18). Nonbenzodiazepine sedative-hypnotic agents promote sleep onset and continuity without altering sleep architecture. They can safely be used in patients with OSA, especially those already using CPAP (19). We

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OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
NOV 2009		**00-00-2009 to 00-00-2009**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Effects of a Short Course of Eszopiclone on Continuous Positive Airway Pressure Adherence	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Walter Reed Medical Center,Pulmonary, Critical Care and Sleep Medicine,6900 Georgia Avenue Northwest,Washington,DC,20307**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**Same as Report (SAR)**	**8**	

hypothesized that a short course of the nonbenzodiazepine sedative-hypnotic eszopiclone during the first 2 weeks of treatment would improve patients' initial tolerability and use of CPAP and subsequently increase long-term adherence.

Context

Approaches that improve adherence to continuous positive airway pressure (CPAP) therapy are needed.

Contribution

In this trial, 160 adults with severe obstructive sleep apnea were randomly assigned to eszopiclone or placebo for the first 14 nights of CPAP. Adherence to CPAP was then measured weekly for 24 weeks. Patients receiving eszopiclone were less likely to discontinue CPAP and used CPAP more nights and for longer periods per night than did patients receiving placebo.

Implication

Eszopiclone given during the first 2 weeks of therapy may help improve long-term adherence and use of CPAP in some patients with severe obstructive sleep apnea.

—The Editors

METHODS

Study Design Overview

We conducted a parallel-design, randomized, placebo-controlled trial to assess the effects of eszopiclone on CPAP adherence among patients with newly diagnosed OSA who were initiating CPAP. Patients received eszopiclone, 3 mg, or matching placebo every night for the initial 14 nights of CPAP and were followed serially for 24 weeks (**Figures 1** and **2**). Patient enrollment began in March 2007, and final data were collected by December 2008. Our study is part of the CPAP ASAP (CPAP Promotion and Prognosis—The Army Sleep Apnea Program) Trial, which will examine several outcomes related to OSA.

Walter Reed Army Medical Center's Department of Clinical Investigation (Scientific Review Committee, Human Use Committee, and Institutional Review Board), as well as the United States Army Center for Investigational Research Organization, approved our protocol. We obtained informed consent from all study participants.

Settings and Participants

We recruited all patients from a single academic sleep medicine center. Our center is part of Walter Reed Army Medical Center, which is a quaternary-care facility providing care to a wide range of patient demographic groups, including active-duty service members, their dependents, and retirees. Consecutive patients between 18 and 64 years of age, with newly diagnosed OSA, and not previously receiving CPAP therapy were approached for enrollment. Obstructive sleep apnea was diagnosed on the basis of an attended, overnight level I polysomnography in all patients. All polysomnograms were interpreted by the study investigators and authors. We established the diagnosis and defined the severity of OSA in accordance with American Academy of Sleep Medicine criteria by using the apnea–hypopnea index (20). We excluded patients with long-term use of hypnotic medications, those who consumed more than 2 alcoholic beverages per night, and those who had hepatic dysfunction or an underlying psychiatric condition that would preclude completion of the study. We also excluded pregnant women.

Randomization and Interventions

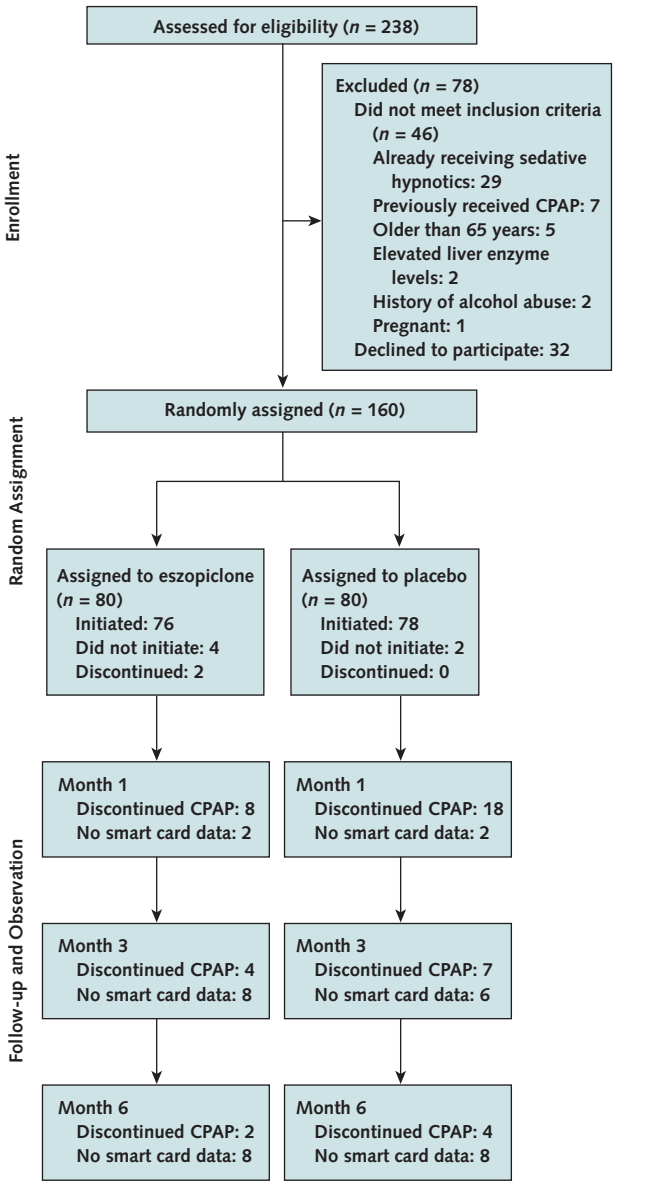
We randomly assigned patients to receive eszopiclone, 3 mg ($n = 80$), or matching placebo ($n = 80$). The Walter Reed Army Medical Center's investigational pharmacy centrally administered and distributed study medications to the patients at the time of enrollment. The referring physician, investigators, and patients were blinded to the randomization order and treatment group assignment (eszopiclone or placebo). Randomization was implemented by using a computerized program (Randomization.com, seed 3565) and was performed by using 16 fixed blocks (10 patients per block) without stratification by patient criteria or polysomnogram results. The pharmacy maintained randomization and blinding until after the final data were collected.

All persons initiating CPAP at our institution participate in a comprehensive educational program to familiarize them with OSA, its effects, and the available treatment options. Patients undergo formal mask-fitting and receive telephone follow-up after 2 weeks to ensure proper fit. A clinical evaluation is conducted after 1 month of therapy to measure CPAP use and assess clinical response to therapy. Additional follow-up is provided as needed. Nonpharmacologic interventions, including changes in pressures, assessment of leaks, mask changes, or adjustments to and education on proper sleep hygiene and stimulus control, are individualized to promote better CPAP tolerance and adherence. All patients enrolled in this study were also assessed after 3 and 6 months of therapy. Otherwise, study participants were not treated differently from other patients receiving care at our center.

After the initial 4 weeks of enrollment, open-label sedatives could be prescribed at the discretion of the physician seeing the patient during follow-up. It is common practice for providers in our clinic to offer a sedative-hypnotic agent to patients who are having difficulties using the CPAP machine despite nonpharmacologic interventions.

All enrolled patients received the same model of CPAP (RemStar Pro M Series with C-Flex and integrated heated humidifiers, Phillips Respironics, Murrysville, Pennsylvania). We prescribed CPAP devices for long-term use. We did not use any autoadjustable positive airway pressure devices.

Figure 1. **Study flow diagram.**



CPAP = continuous positive airway pressure.

Outcomes and Measurements

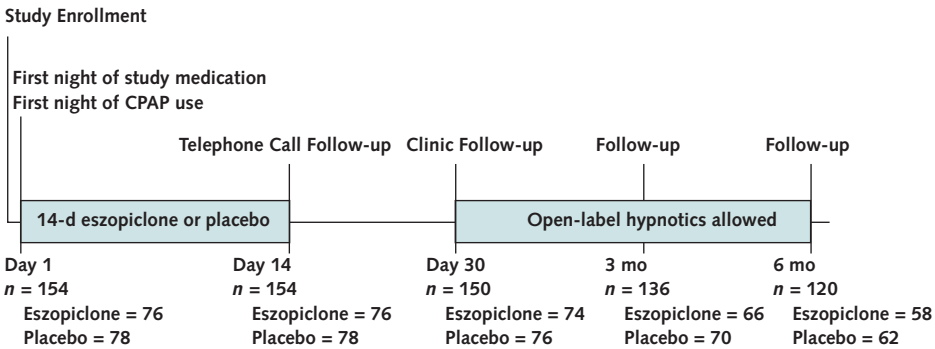
For each participant, we recorded demographic data, information regarding OSA severity, degree of symptoms, and objective measures of CPAP use. The primary outcome measured was CPAP adherence at 24 weeks. Specifically, we computed the percentage of nights used, the mean hours per night for total study nights, and the mean hours per night that CPAP was used during each week of the 24-week study. We also compared the rate of "regular use of CPAP" between groups, defined as more than 4 hours per night on more than 70% of nights (21). We obtained objective measures of CPAP use from a downloadable "smart card" adherence-monitoring device (Encore Pro smart card, Phillips Respironics). These cards, which are integrated into the CPAP units, record all use of the device—specifically, the date, time, and duration that CPAP is used. These cards also record data on mask leaks and residual airflow limitations, data that are useful to troubleshoot barriers to therapeutic adherence. We collected all measured variables at the time of enrollment (baseline) and again at 1, 3, and 6 months after initiating CPAP. In addition, we collected smart cards at 1, 3, and 6 months and recorded and analyzed the downloaded data for each night in 1-week blocks.

Secondary outcomes were the rate of CPAP discontinuation and the use of open-label sedative-hypnotic agents between the 2 groups. Because our primary aim was to promote better CPAP adherence, we allowed the open-label use of sedative-hypnotic agents after the first 4 weeks of treatment. These were prescribed at the discretion of the ordering physician and only when nonpharmacologic interventions were unsuccessful. All such prescriptions were monitored and recorded by using a closed electronic medical records system. In addition, we compared the change in Epworth Sleepiness Scale (ESS) score, fatigue, and Functional Outcomes of Sleep Questionnaire score between baseline and the end of the study to determine whether a greater use of CPAP was associated with improvements in symptoms and quality of life. We assessed degree of somnolence by using the ESS and visual analogue fatigue scale (22). The ESS score ranges from 0 to 24. Higher scores indicate greater daytime somnolence, and scores less than 10 are considered normal. We assessed sleep-related quality-of-life scores by using the Functional Outcomes of Sleep Questionnaire (23). The score ranges from 5 to 20. Higher scores, particularly those greater than 17.9, suggest improved quality of life. We collected additional data related to mood and depression, libido and erectile dysfunction, and quality of life that will be included in subsequent papers.

Follow-up Procedures and Monitoring

We obtained serial evaluations and data collection as described previously. We monitored and recorded potential adverse reactions and adherence to the study medication. Study participants received a telephone call at the end of the 2-week treatment and were asked whether they had or had not experienced headaches, dizziness, residual daytime somnolence, confusion, rash, or an unpleasant aftertaste. Study participants also could report any other potential reaction in an open-ended format. We recorded both the occurrence and severity of these potential symptoms. Investigators obtained a similar assessment during each serial follow-up visit for any person using open-label sedative-hypnotic agents. Potential side effects were discussed with the study's medical monitor, and patients were permitted to disenroll at their discretion without compromising the follow-up and continued care they would have received as part of this trial.

Figure 2. **Study design overview.**



CPAP = continuous positive airway pressure.

Statistical Analysis

Data are presented as means (SDs), and *P* values less than 0.05 were considered to represent statistical significance. For all analyses, when patients turned in their smart card but had no CPAP use documented, adherence was listed as zero. If absence of use was verified per patient report, adherence was also listed as zero. When patients stopped providing data before the 6-month follow-up visit, we calculated percentage of nights used by using the last week of follow-up as the denominator. For assessment of hours per total nights, we assumed zero use on all nights that could not be verified. For the assessments of regular use and for the longitudinal analyses, we assumed that patients who had incomplete follow-up had discontinued therapy.

We assessed the effects of eszopiclone on adherence during follow-up by using the generalized estimating equations approach. We assumed that outcome variables for the 24-week study (percentage of nights used, mean hours per night for total study nights, and mean hours per night that CPAP was worn) had normal distribution. The generalized estimating equation used generalized linear models and quasi-likelihood methods, allowing for an unequal number of observations between participants. We specified an identity link and exchangeable working correlations for the analysis. Age, apnea–hypopnea index, and ESS score at baseline were included as covariates in the models. We analyzed time to discontinuation and time to cessation by using Cox proportional hazards regression models. We added age, apnea–hypopnea index, and baseline ESS score as covariates. We analyzed data by using the PASW Statistics 17 (formerly SPSS Statistics 17.0, SPSS, Chicago, Illinois).

Role of the Funding Source

This investigator-initiated project was conducted by using an unrestricted research grant and study medications provided by Sepracor to the Henry M. Jackson Foundation for the Advancement of Military Medicine. Sepracor had no role in the study design, patient enrollment, data collection or interpretation, and manuscript preparation or in the decision to submit the manuscript for publication.

RESULTS

Of 160 enrolled patients, 154 received the study drug (76 received eszopiclone and 78 received placebo) and were included in analyses. Of the enrolled patients, 150, 136, and 120 completed follow-up at 1, 3, and 6 months, respectively (**Figures 1** and **2**). Baseline patient characteristics of patients in the 2 groups were similar (**Table 1**). No protocol violations or crossovers occurred between groups. Reported side effects from study medications were uncommon and did not differ between groups (**Table 2**).

Among the entire cohort, CPAP was used on 61.7% of nights during follow-up. Mean nightly use was 3.0 hours (SD, 2.6) for all patients. Eszopiclone resulted in improvements in CPAP adherence. Patients receiving eszopiclone used CPAP for 64.4% of nights compared with 45.2% in those receiving placebo (difference between groups, 20.8 percentage points [95% CI, 7.2 to 34.4 percentage points]; $P = 0.003$). In the eszopiclone and placebo groups, CPAP was used for 3.57 versus 2.42 hours per night for all study nights (1.3 hours [CI, 0.4 to 2.2 hours]; $P = 0.005$) and for 4.05 versus 3.02 hours for nights when CPAP was used (1.1 hours [CI, 0.2 to 2.1

Table 1. **Baseline Characteristics**

Characteristic	Eszopiclone (*n* = 76)	Placebo (*n* = 78)
Mean age (SD), *y*	46.8 (7.8)	44.6 (6.6)
Men, %	74.7	82.3
Mean BMI (SD), kg/m^2	30.3 (3.8)	30.4 (4.2)
Mean ESS score (SD)	12.1 (4.3)	12.7 (4.2)
Mean fatigue (SD)*	5.7 (1.5)	6.0 (1.5)
Mean FOSQ score (SD)	14.8 (2.7)	14.7 (3.3)
Mean sleep latency (SD), *min*	23.1 (22.5)	23.3 (19.5)
Mean sleep latency >30 min, %	18.7	20.8
Mean apnea–hypopnea index (SD), *events/h*	35.8 (24.1)	36.9 (22.3)
Mean prescribed CPAP (SD), *cm* H_2O	10.8 (2.4)	10.5 (2.4)

BMI = body mass index; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire.
* Measured on a visual analogue scale.

Table 2. **Adverse Events***

Adverse Event	Eszopiclone (*n* = 76)	Placebo (*n* = 78)
Reported side effect, *n*	6 (7.9%)	5 (5.1%)
Death	0	0
Serious event	0	0
Minor event		
Bitter taste	2	2
Grogginess	1	0
Dry mouth	1	1
Headaches	0	1
Anxiety	1	1
Drowsiness	0	1
Withdrawal due to adverse event, *n*	2†	0

* All adverse events occurred within the first week of treatment.
† Both withdrawals occurred after 2 days of treatment.

hours]; $P = 0.019$) (**Figure 3**). Missing data due to participants not returning their smart card ranged from 2% at week 1 (4 of 154 patients) to 22% at week 24 (34 of 154 patients). Missing data were equally distributed between groups at any week (Fisher exact test *P* value ranged from 0.40 to 1.00); 87.4% of the total data points ($n = 3696$) were available for inclusion in the models. Addition of covariates (age, apnea–hypopnea index, and baseline ESS score) to the model did not change the results. When we excluded the 34 patients who did not complete the full 24-week follow-up and reanalyzed our data by using the generalized estimating equation approach, statistically significant differences in favor of eszopiclone remained.

Time to stopping regular use of CPAP (regular use was defined as use for >4 hours/night for >70% of nights) was shorter with placebo than with eszopiclone. The mean duration of regular use of CPAP was 13.3 weeks for the placebo group and 17.6 weeks for the eszopiclone group (hazard ratio, 1.91 [CI, 1.21 to 3.01]; $P = 0.005$). Of those who discontinued therapy, the mean time to discontinuation of CPAP for the placebo and eszopiclone groups was 17.2 weeks and 19.7 weeks, respectively (hazard ratio, 1.90 [CI, 1.1 to 3.4]; $P = 0.033$). No covariates (age, apnea–hypopnea index, and baseline ESS score) were associated with time to discontinuation of CPAP or cessation of regular use; therefore, we excluded them from the final model. During the final week of the observation period, CPAP was used for more nights (62.2% vs. 36.5%; $P = 0.001$) and for more hours per night (4.2 hours [SD, 2.6] vs. 2.7 hours [SD, 2.7]; $P = 0.010$) in the eszopiclone group. In addition, more patients in the eszopiclone group met our definition for regular CPAP use during the final month of observation (48% vs. 25%; $P = 0.003$).

Use of CPAP resulted in subjective improvements. Compared with baseline, the ESS score decreased by 22.7% in the eszopiclone group versus 7.6% in the placebo group (difference, 15.1 percentage points [CI, 0.29 to 29.9 percentage points]; $P = 0.046$), fatigue decreased by 17.7% versus 10.2% (difference, 7.49 percentage points [CI, −7.16 to 22.15 percentage points]; $P = 0.31$), and the Functional Outcomes of Sleep Questionnaire total score increased by 12.6% versus 9.4% (difference, 2.54 percentage points [CI, −9.54 to 4.45 percentage points]; $P = 0.47$).

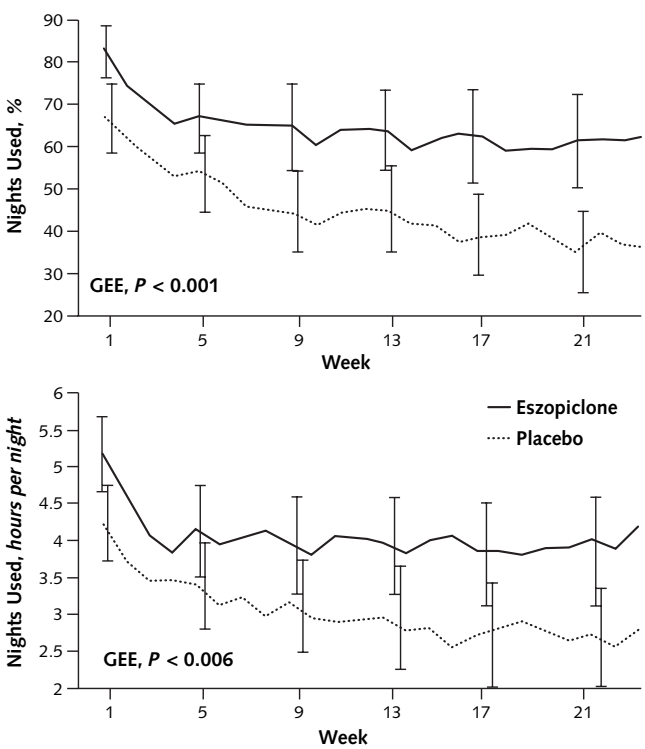
A total of 38 patients (24.7%) requested open-label nonbenzodiazepines. This request was more frequent among those receiving placebo than CPAP (31% vs. 19%; $P = 0.084$). The mean duration of hypnotic use (9.7 days [SD, 2.1]) was similar for both groups.

Assuming that therapy was discontinued in all patients who did not complete their final follow-up visit, CPAP therapy had been discontinued by 77 patients (50.0%) and was more common among those receiving placebo (57.7% vs. 42.1%; $P = 0.054$). Of those who stopped therapy, 39.0% did so within the first month of use. The difference in discontinuation was evident at 1 week and continued to increase for the duration of the study.

DISCUSSION

A 2-week course of eszopiclone during the initiation of treatment increased CPAP adherence for the first 6 months of therapy. The medication was well tolerated with very few reported side effects. Use of CPAP resulted in improvements in subjective sleepiness, fatigue, and quality of

Figure 3. **Continuous positive airway pressure use.**



GEE = generalized estimating equation.

life. These improvements were greater in the eszopiclone group, probably reflecting the increased use of CPAP.

Despite a short course of sedatives, improvements in therapeutic adherence persisted long after discontinuation of the study medications. Sedation probably facilitated better comfort with CPAP, which may have improved tolerance. Many persons experience poor sleep quality during the transition to CPAP, which can create a negative conditioning response that impairs their willingness to continue. Improving the initial experience with CPAP may facilitate a successful transition. Interventions aimed at improving this initial treatment period should lead to improved long-term adherence. For this reason, we chose to provide sedatives during the first 2 weeks of CPAP use.

We conducted a MEDLINE search to identify previous studies aimed at improving CPAP adherence or initial tolerance of therapy. In a similar study, Bradshaw and associates (24) assessed the utility of zolpidem for improving CPAP adherence. Although they did not find an effect, their study and ours had important differences that may explain the discordant results. Their study enrolled a limited number of patients (24 in each group) and may not have been adequately powered to detect a difference between the intervention and control groups. They also did not regulate the use of hypnotics during the first month and, therefore, did not include a standardized treatment group. The lack of measured benefits in their study may reflect their choice of a nonbenzodiazepine hypnotic. Although effective at inducing sleep, zolpidem has a shorter half-life and may not promote sleep continuity for the entire night. We selected the longer-acting agent, eszopiclone.

Several interventions intended to improve CPAP adherence have been previously assessed. Those that have shown promise share the similar focus of improving comfort with therapy. Quieter devices coupled with better-fitting masks improve patient tolerance and subsequent adherence (25). Newer machines provide a more-comfortable delivery of pressure with variable airflows, adjustable settings, and integrated heated humidifiers, all designed to improve patient comfort (26). For many medical conditions, a patient-focused approach that emphasizes education, close follow-up, and patient participation in treatment has improved adherence to prescribed medical therapy. Although these strategies may have a modest effect on CPAP adherence, they all require substantial time and expense (27–29). Whether this allocation of resources is cost-effective is a matter of debate.

Nonbenzodiazepine sedative-hypnotic agents are effective for inducing sleep. In addition, they may be used safely in patients with underlying sleep-disordered breathing, without resulting in an increase in respiratory events or significant reductions in the Sp_{O_2} nadir (19, 30, 31). In a recent retrospective review (32), the use of nonbenzodiazepine sedative-hypnotic agents during the in-laboratory CPAP titration study was the only variable shown to predict subsequent adherence. The improvements in adherence seen in this review and in our current study may be the result of a better initial experience with CPAP.

Our study has several limitations. One quarter of our cohort did not complete the full 24-week follow-up. To minimize the effects of this potential bias, we analyzed adherence data with these persons included (intention-to-treat analysis), assuming zero use of CPAP for all missing data points. This may actually lead to an underestimation of eszopiclone's effect on adherence. We did not qualitatively survey patients regarding CPAP tolerance, so we can only theorize on the mechanism by which eszopiclone facilitated better adherence. However, the effect on the objectively measured end point of CPAP adherence was clear. Although far from ideal, adherence rates in our cohort were higher than those reported by others (33). Because a percentage of patients with OSA may also have insomnia, the presence of insomnia at baseline could bias our results. We attempted to control for this via self-reports of sleep latency at baseline. Mean sleep latency or the percentage of patients with sleep latency exceeding 30 minutes was no different between the 2 groups. No correlation existed between sleep latency at baseline and subsequent adherence, as measured by percentage of nights used or hours used per total study nights. However, we cannot exclude the possibility that the difference in effect was caused by undertreated insomnia in the placebo group, as opposed to an improvement in CPAP acceptance in the intervention group. As a group, the cohort reported relatively long sleep latencies. The benefits observed may be biased by the presence of difficulty with sleep initiation. We could not identify subpopulations, such as patients with concomitant insomnia, who would benefit more from this intervention, and further studies are needed to make this determination. Finally, we did not restrict the use of sedative-hypnotic agents after the first month of CPAP. The subsequent use of sedative-hypnotic agents did not differ between groups but tended to be higher in patients receiving placebo. This may have diluted the treatment effect of eszopiclone.

As the prevalence of OSA and the demand for CPAP continue to increase, fewer resources will be available for patients. In addition, the growing burden of disease is quickly shifting the treatment from the subspecialist to the primary care physician. Simple interventions that can reliably improve therapeutic adherence are needed. Our findings show that a short course of the nonbenzodiazepine sedative-hypnotic eszopiclone given during the initial 2 weeks of CPAP use improved subsequent adherence to CPAP at 6 months. Because of the poor adherence to CPAP in many patients, any simple intervention that can reliably increase use should be considered. A short course of nonbenzodiazepines is a simple option that may facilitate better CPAP tolerance, improve therapeutic adherence, and reduce the rate of self-discontinuation of therapy.

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Disclaimer: The views expressed in this article are solely the authors and do not reflect those of the government nor constitute official policy of the United States Army or Department of Defense.

Acknowledgment: The authors thank the participants for their involvement in the trial. They also thank research assistant Rachel Massey and respiratory therapist Sandra Clay for their valuable contributions to the study.

Grant Support: By Sepracor to the Henry M. Jackson Foundation for the Advancement of Military Medicine.

Potential Conflicts of Interest: None disclosed.

Reproducible Research Statement: *Study protocol*: Available online at ClinicalTrials.gov or from Dr. Lettieri (christopher.lettieri@us.army.mil). *Statistical code:* Available from Dr. Holley (aaron.holley@amedd.army.mil). *Data set*: Available from Dr. Lettieri.

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